binding agent is an immunoglobulin single variable domain, more preferably the binding agent is derived from a heavy chain antibody. Most preferably, the binding agent is a Nanobody.

[0011] Also envisaged is a polypeptide, comprising the above-described binding agent.

[0012] In one embodiment, the above-described binding agent may also be immobilized on a solid support.

[0013] In another aspect, the disclosure relates to a complex comprising muscarinic receptor M2 (M2R) and a conformation-selective M2R binding agent. The complex may further comprise at least one other conformation-selective receptor ligand. Also, the complex may be crystalline. In a further aspect, the disclosure also encompasses a composition comprising the above-described complex. Such a composition may be any composition, but preferably is a cellular composition or a membrane composition.

[0014] Further, the disclosure relates to a nucleic acid molecule comprising a nucleic acid sequence encoding an amino acid sequence of any of the above-described binding agents. Also envisaged is a host cell, comprising a nucleic acid sequence of the disclosure.

[0015] The above-described conformation-selective compounds targeting muscarinic receptor M2 can be used in a range of applications, including capturing and/or purification of receptor in a functional conformation, ligand screening and (structure-based) drug discovery, crystallization studies, but also as therapeutic or diagnostic agents.

[0016] Other applications and uses of the amino acid sequences and polypeptides of the disclosure will become clear to the skilled person from the further disclosure herein.

BRIEF DESCRIPTION OF THE DRAWINGS

[0017] The skilled artisan will understand that the drawings, described below, are for illustration purposes only. The drawings are not intended to limit the scope of the present teachings in any way.

[0018] FIGS. **1**A and **1**B: Results of selection of M2 Gi mimetic nanobodies from a post-immune llama VHH library.

[0019] FIG. **2**: Summary of sequences of selected M2 Gi mimetics and their effect on an M2 receptor radioligand binding assay. As a non-limiting example, Nb9-8, causes a substantial enhancement of iperoxo affinity in a competition binding assay, similar to the G protein G_i. Nb9-8 is SEQ ID NO:1; Nb9-1 is SEQ ID NO:2; Nb9-11 is SEQ ID NO:3; Nb9-7 is SEQ ID NO:4; Nb9-22 is SEQ ID NO:5; Nb9-17 is SEQ ID NO:6; Nb9-24 is SEQ ID NO:7; Nb9-9 is SEQ ID NO:8; Nb9-14 is SEQ ID NO:9; Nb9-2 is SEQ ID NO:10; Nb9-20 is SEQ ID NO:11.

[0020] FIGS. **3**A-**3**C: Results of selections for functional M2 nanobody ligands from a postimmune llama VHH library using the Gi mimetic Nb9-8.

[0021] FIG. **4**: Summary of sequences of selected functional, extracellular M2 nanobody ligands and their effect on M2 receptor in a radioligand binding assay.

[0022] FIG. **5**: The overall structure of the active-state Mz receptor (orange) in complex with the orthosteric agonist iperoxo and the active-state stabilizing nanobody Nb9-8 is shown.

[0023] FIG. **6**: Data collection and refinement statistics.

DEFINITIONS

[0024] The disclosure will be described with respect to particular embodiments and with reference to certain drawings but the disclosure is not limited thereto but only by the claims. Any reference signs in the claims shall not be construed as limiting the scope. The drawings described are only schematic and are non-limiting. In the drawings, the size of some of the elements may be exaggerated and not drawn on scale for illustrative purposes. Where the term "comprising" is used in the present description and claims, it does not exclude other elements or steps. Where an indefinite or definite article is used when referring to a singular noun, e.g., "a" or "an," "the," this includes a plural of that noun unless something else is specifically stated. Furthermore, the terms first, second, third and the like in the description and in the claims, are used for distinguishing between similar elements and not necessarily for describing a sequential or chronological order. It is to be understood that the terms so used are interchangeable under appropriate circumstances and that the embodiments of the disclosure described herein are capable of operation in other sequences than described or illustrated herein.

[0025] Unless otherwise defined herein, scientific and technical terms and phrases used in connection with the disclosure shall have the meanings that are commonly understood by those of ordinary skill in the art. Generally, nomenclatures used in connection with, and techniques of molecular and cellular biology, structural biology, biophysics, pharmacology, genetics and protein and nucleic acid chemistry described herein are those well-known and commonly used in the art. Singleton, et al., *Dictionary of Microbiology and Molecular Biology,* 2D ED., John Wiley and Sons, New York (1994), and Hale & Marham, *The Harper Collins Dictionary of Biology*, Harper Perennial, NY (1991) provide one of skill with general dictionaries of many of the terms used in this disclosure. The methods and techniques of the disclosure are generally performed according to conventional methods well known in the art and as described in various general and more specific references that are cited and discussed throughout the present specification unless otherwise indicated. See, for example, Sambrook et al., *Molecular Cloning: A Laboratory Manual,* 3th ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., (2001); Ausubel et al., *Current Protocols in Molecular Biology,* Greene Publishing Associates (1992, and Supplements to 2002); Rup, Biomolecular crystallography: principles, *Practice and Applications to Structural Biology,* 1st edition, Garland Science, Taylor & Francis Group, LLC, an informa Business, N.Y. (2009); Limbird, *Cell Surface Receptors,* 3d ed., Springer (2004).

[0026] As used herein, the terms "polypeptide," "protein," "peptide" are used interchangeably herein, and refer to a polymeric form of amino acids of any length, which can include coded and non-coded amino acids, chemically or biochemically modified or derivatized amino acids, and polypeptides having modified peptide backbones. Throughout the application, the standard one letter notation of amino acids will be used. Typically, the term "amino acid" will refer to "proteinogenic amino acid," i.e., those amino acids that are naturally present in proteins. Most particularly, the amino acids are in the L isomeric form, but D amino acids are also envisaged.

[0027] As used herein, the terms "nucleic acid molecule," "polynucleotide," "polynucleic acid," "nucleic acid" are